REMARKS

Amendment of claims herein is made without prejudice to the applicants' right to pursue claims of the same or similar scope in a duly filed continuing application.

The subject matter of new claims added herein is fully supported by the specification (support indicated below as found in the published application).

The subject matter of new claim 70 reciting the protamine fragment is a protease cleavage product is supported at paragraphs 0106 through 0110 and paragraph 0141.

The subject matter of new claim 71 reciting the protamine fragment is cleaved by a protease which is thermolysin is supported at paragraph 0108 and 0141, ficin at paragraph 0109, collagenase at paragraph 0110, kallikrein at paragraph 0110 and proline-specific endoprotease at paragraph 0110.

The subject matter of new claim 72 reciting the protamine fragment being derived from a protamine which is either salmon protamine is supported as paragraph 0105 or clupine protamine is also supported at paragraph 0105.

The subject matter of new claim 73 reciting the amino acid composition of the protamine fragment to comprise five or six arginine amino acid residues and 1 proline amino acid residue is supported at paragraph 0154.

The subject matter of new claim 74 reciting the protamine fragment to have a minimum of six arginine amino acid residues is supported at paragraph 0155.

The new claims therefore include no new matter.

The Rejection of Claims under 35 USC §112, First Paragraph

The examiner maintained rejection of all pending claims under 35 USC §112, first paragraph, asserting that the claimed subject matter lacked written descriptive support in the specification. In response to the applicants' amendment of the claims to recite that the modified protamine utilized is a protamine fragment, the examiner alleged that no structural limitations are provided regarding the fragment, and while the claims recite a "modified protamine," the claims assertedly do not establish what the modifications are. The examiner

asserted that a skilled artisan cannot envision the detailed chemical structure of the recited protamine fragment and thus the genus of fragments are allegedly not adequately described.

The applicants respectfully disagree with the rejection.

Firstly, the applicants direct the examiner's attention to the recited molecular weight range of the protamine fragment utilized in the recited method. If it is accepted, as asserted by the examiner at page 6 of the office action, that protamine structure comprises 31 amino acid residues, and the average molecule weight of an amino acid is between 110 and 115 daltons (stated without evidence, but can be supported if the examiner requests such evidence), then full length protamine has a molecular weight of approximately 3410 daltons to approximately 3565. Thus, the worker of ordinary skill would readily appreciate that the claims are directed to methods which,. In the broadest recitation, utilize a protamine fragment that is approximately 12% to approximately 73% the size of the full length protein is full length protamine is approximately 3410 daltons, or approximately 11% to approximately 70% the size of full length protamine if full length protamine is approximately 3565 daltons. The applicants submit that this molecular weight range clearly distinguishes the protamine fragments recited in the claimed methods.

More importantly, however, the focus of a written description inquiry should be to look to *whatever is now claimed*, and whether the inventors had possession of the claimed subject matter. Here, the applicants submit that each of the rejected claims is drawn to a *method,* a patentable category of subject matter that is distinct from the category of *compositions* (see 35 U.S.C. §101). More specifically, the claims in question here recite *methods of use* subject matter and not specific proteins or protein sequences. As stated in the Federal Register when the current Written Description Guidelines were promulgated "[t]he description need only describe in detail that which is new or not conventional." (See 66 FR 1106). It is beyond question that the specification teaches and describes methods of inactivating (or neutralizing) heparin using one or more protamine fragments having a molecular weight between about 400 and about 2500 daltons. See, e.g., Example 1, paragraph 0145 et seq., and Example 2, paragraph 0175 et seq., both numbered as in the published application. Thus, the novelty lies in the inactivation of heparin with specifically recited low molecular weight protamine fragments. The point of contention, however, revolves around whether the specification shows possession of methods that employ

protamine fragments defined by some structural feature that also possess the recited activity/property. The applicants submit that the specification does provide such a teaching.

In the first instance, Example 1 teaches preparation of low molecular weight protamines (LMWP) (paragraphs 0140 - 0141) with the ability of these LMWP to neutralize heparin and which lack immunogenicity of full length protamine. For example, paragraphs 0152 through 0154 teach that proteolytically-cleaved protamine was able to neutralize heparin as effectively as full length protamine, with results set out in Figs 2 and 3. Paragraph 0158 demonstrates that the LMWP exhibited none of the antibody production associated with full length protamine in an *in vivo* mouse model, the results being set out in Fig. 7. Of further significance, this example teaches how one skilled in the art would prepare a LMWP having these properties and the assays described above teach how to identify one.

In another instance Example 2 shows that a commercially available LMWP (Sanofi Recherche, Gentilly Codex, France, described in paragraph 0176) was able to neutralize anticoagulant function of heparin (paragraph 0178) and induce less complement activation than full length protamine (paragraph 0180).

Thus, the specification teaches not only preparation of LMWP recited in the claimed methods, but also where such LMWP can be commercially obtained.

Combining these disclosures with the fact that full-length protamine is known in the art and its amino acid sequence understood (see for example, the instant office action at the paragraph bridging pages 6 and 7 wherein the examiner sets forth common knowledge in the art, as well as paragraphs 0103 through 0110 in the published application), it must be concluded that the specification expressly contemplates methods of inactivating heparin with protamine fragments having low level immunogenicity (compared to full length protamine) as recited in the rejected claims.

The Federal Register in discussing the Written Description Guidelines recognized that an applicant can show possession of the claimed invention by describing distinguishing, identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. (See 66 FR 1104, col. 3.) "An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." (66 FR 1105, col. 3.) In the case of the presently claimed *methods*, the

distinguishing characteristic is not the structural characteristics of LMWP compounds *per se* (*i.e.*, the protein sequence) even though the protamine fragments are clearly distinguished by the recited molecular weights, but rather the steps of the inactivating heparin using a protamine fragment having a specific molecular weight. See 66 FR 1106, cols. 1-2, distinguishing structures of products from steps of a process. Examples 1 and 2 make is unambiguously clear that the applicants were in possession of such a method.

The instant facts are on point with the facts in Example 18 of the Revised Interim Written Description Guidelines ("the Guidelines" found at www.uspto.gov/web/menu/written.pdf), which provides guidance to as to how to approach a "process claim where the novelty is in the method steps." In this Example 18, the specification was found to have taught a method for producing proteins in *Neurospora crassa*. In the method, mitochondria were isolated from this fungus and transformed with a mitochondrial expression vector which comprises a nucleic acid encoding a protein of interest. The protein was subsequently expressed and isolated from the mitochondria. The specification exemplified the expression of α-galactosidase by the claimed method using a cytochrome oxidase promoter. The claim in question read:

> "A method of producing a protein of interest comprising;
> obtaining Neurospora crassa mitochondria,
> transforming said mitochondria with a expression vector
> comprising a nucleic acid that encodes said protein of interest,
> expressing said protein in said mitochondria, and recovering
> said protein of interest."

In analyzing the claim, the Guidelines recognized that the sequence of the nucleic acid is not essential to the claimed invention and a search of the prior art revealed that the claimed method of expression in *Neurospora crassa* is novel and unobvious. The same is true here in that no art has been cited against the claimed subject matter.

Next, the Guidelines explained that the claim in Example 18 was drawn to a genus, *i.e.*, any of a variety of methods that can be used for expressing protein in the mitochondria and there was an actual reduction to practice of a single embodiment, *i.e.*, the expression of α-galactosidase. Likewise, the claims of the instant invention are drawn to a genus of heparin inactivation methods utilizing fragments of known proteins which possess inactivation activity the same as or similar to that of full length protein, but which induce a lower immune response. Also as in Example 18, actual reduction to practice is demonstrated with various

protamine fragments (*i.e.*, more examples than in the Guidelines Example 18), and there are a limited number of ways of practicing the process steps of the claimed methods (*i.e.*, there are a limited number of protamine fragments). As in Example 18 of the Guidelines, the embodiments of the claimed methods are disclosed in Examples 1 and 2 in the application and are therefore representative of the genus and demonstrate reduction to practice, *i.e., possession by the inventors is shown*. Therefore, if the instant claims are analyzed as method claims consistent with guidance presented in the Guidelines, the claimed invention must be found to be adequately described.

In view of the above discussion, Applicants respectfully submit that the rejection of claims under 35 U.S.C. §112, first paragraph for lack of written description is overcome and that the rejection should be withdrawn. Further, the applicants submit that the rejection cannot apply to any of the new claims added herein in that the new claims further define a LMWP utilized in the claimed method.

CONCLUSION

In view of the amendments and remarks made herein, the applicants believe that all claims are now in condition for allowance and respectfully request notification of the same.

Dated: March 27, 2008

Respectfully submitted,

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